Nitrosamines

1937 Freund reported the hepatotoxic action of *N*-nitrosodimethylamine in describing the clinical and autopsy findings in two chemists accidentally poisoned with N-nitrosodimethylamine. [1]

1956 During an investigation of factors that might be responsible for liver damage in industrial workers, Magee and Barnes discovered that the feeding of dimethylnitrosamine (DMNA) to rats led to hepatic tumors. [2]

1961 Dontenwill and Mohr data indicated that diethylnitrosamine (DENA) has organ-specific tumorigenic effect in the tracheobronchial tree of hamsters. [3]

1961 Druckrey *et al.* conducted the first major study of the formation, chemical structure, and carcinogenicity of *N*-nitrosamines. [4]

1962 Druckrey and Preussmann suggested that conditions were suitable for the formation of nitrosamines in tobacco smoke, based on the fact that secondary amines and nitrogen oxides, both of which are in tobacco smoke, combine to form nitrosamines *in vitro*. [5]

1963 Herrold and Dunham reported that intratracheal or intragastric administration of nitrosodiethylamine yielded a large number of tumors in the respiratory tract. [6]

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1963 Boyland *et al.* discussed the possibility of the presence of nitrosamines in tobacco smoke, particularly "in the acidic environment of the cigarette smoke" as opposed to cigar and pipe smoke. [7]

1964 Serfontein claimed to find up to 100 micrograms of nitrosopiperidine in the mainstream smoke of 100 cigarettes. [8]

1964 Robertson, President of the National Cancer Association of South Africa, commenting on Serfontein and Hurter's report of identifying nitrosamines in cigarette smoke, said "[t]he significance of this discovery lies in the fact that although the nitrosamine compound is known as a carcinogen, this is the first time that it has been established beyond doubt that various nitrosamines occur in cigarette smoke." [Emphasis supplied]. [9]

1964 Boyland, Gorrod, Roe and Mitchley suggested, in the 41st Annual Report of the British Empire Cancer Campaign (covering 1963), that it was possible, because of the formation of nitrosamines by the reaction of oxides of nitrogen with secondary amines, that cigarette smoke could contain nitrosoanabasine and nitrosonornicotine. The authors also note that nitrosoanabasine produced many tumors of the esophagus when administered orally to rats. [10]

1966 Serfontein and Hurter, testing nonfilter South African cigarettes, found that "in the course of initial scanning experiments, strong evidence was obtained by means of gas chromatographic analysis of the neutral fraction of a cigarette smoke condensate ... that various nitrosamines [*N*-nitrosopiperidine, *N*-nitrosodimethylamine and *N*-nitrosodiethylamine] were present in cigarette smoke in measurable quantities." [11]

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1967 In a review, Magee and Barnes noted that "[i]t is too early to be able to suggest with any confidence the part nitrosamines might play in the etiology of human cancer. In a whole range of experimental animals tumors can be produced in a number of different sites which bear in some cases a striking pathological resemblance to cancers seen in man. However, the species, the nature of the nitroso compound, and the dose and route by which it is administered can all play a part in determining the nature of the malignant lesion produced." [12]

1967 In Tobacco and Tobacco Smoke, Wynder and Hoffmann noted that "to date, we lack a method of quantitative determination of nitrosamines in tobacco smoke although a few good qualitative techniques have emerged. Since the presence of nitrosamines in cigarette smoke bears considerable implications in tobacco carcinogenesis, it is hoped that further and more detailed studies will also be initiated by other groups to clarify fully this important factor.... [A] most important question, however, is whether nitrosamines are indeed formed during smoking of tobacco and whether the induction of papillary tumors in the respiratory tree of hamsters bears any relation to the induction of human bronchiogenic cancer."

They conclude: "At this time one cannot deny the potential of tobacco smoke to form nitrosamines; however, we are not convinced that these agents actually exist in the cigarette smoke inhaled by man." [13]

1969 Rathkamp and Hoffmann demonstrated that nitrates added to tobacco decreased levels of carcinogenic PAH in smoke (and also the mouse-skin tumorigenicity). Later studies indicated that

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increased nitrate resulted in an increased nitrosamine content [14]

1972 The chapter in the Surgeon General's report dealing with the harmful constituents of cigarette smoke notes that studies reporting the presence of various nitrosamines were published after the June 1970 conference on which the chapter was based. [15]

1974 In an essay, J.M. Barnes stated that "[p]reoccupation with the occurrence and behavior of minute amounts of nitrosamines in the human environment will probably divert skills from more profitable studies of the behavior of nitrosamines in experimental systems....If [the essay] leaves the reader with the impression that nitrosamines have a much greater potential as research tools than they have as health hazards, it will have served its purpose." [16]

1976 "That a wide range of species is susceptible to the carcinogenic action of nitrosamines suggests that man is probably not resistant....Many *N*-nitroso compounds are powerfully carcinogenic in experimental animals, and, although there is no proof, it is highly probable that they are also carcinogenic in man." [17]

1977 Brunnemann, Yu and Hoffmann reported lower values of volatile nitrosamines in mainstream smoke, attributing their reduced levels to avoidance of artifactual nitrosamine formation during smoke collection and analysis. "In fact, several of the cigarettes which were machine smoked earlier and analyzed without precautions, when smoked by us under the same conditions but with precautions, yielded 25 to 100% lower values for DMN and NPY for the mainstream smoke."

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The authors indicate that their data support the idea that the yield of volatile nitrosamines depends on the nitrate content of the tobacco. [18]

1977 The Royal College of Physicians reported that *N*-nitroso compounds were, along with polycyclic aromatic hydrocarbons, the chief initiators of cancer in tobacco smoke. The report notes that "[t]he *N*-nitrosamines in food and drink are regarded as a potential health hazard at concentrations as low as one part per billion. *N*-nitrosonornicotine has been identified in both tobacco smoke and unburnt tobacco, the concentration in the latter being 2,000 to 9,000 parts per billion--concentrations much higher than those of other nitroso compounds found in meat, fish, or beverages. Its presence may be of great biological importance and could explain the correlation between tobacco chewing and the development of cancer of the month." [19]

1979 The U.S. Surgeon General notes that nitrosamine yield is largely determined by the nitrate content of the tobacco and that many nitrosamines are known animal carcinogens. It was also noted that "at present, it has not been demonstrated that there is a significant reduction of the tumorigenic potential of cigarette smoke." [20]

1980 Hoffmann *et al.* noted "In the mainstream smoke of a cigarette, these carcinogens [volatile *N*-nitrosamines] can be reduced significantly by utilization of tobacco low in nitrate content and acetate filtertips that selectively retain volatile *N*-nitrosames." [21]

1980 In describing "[T]he Less Harmful Cigarette," Hoffmann, Tso and Gori include a table showing that nitrate fertilization of tobacco [which leads to increased nitrosamine formation] has led to significant reductions in "tar," nicotine, benzo[*a*]pyrene and

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carcinogenicity. The authors write that "the reduction of the tar content of cigarettes was an important step in reducing the hazards of cigarette smoking." [22]

1982 Wynder and Hoffmann, in an article published in Tabak Journal International, include a table indicating that nitrate fertilization [known to increase the yield of nitrosamines in cigarette smoke] significantly reduced the biological activity (carcinogenicity) of cigarette smoke condensate. [The PAH levels in smoke are also reduced by adding nitrate]. [23]

1982 The report of the U.S. Surgeon General, citing the studies of Magee *et al.* and the International Agency for Research on Cancer (IARC), concludes: "more than 50 of the approximately 100 *N*-nitrosamines which have been tested have various degrees of carcinogenic potency in laboratory animals. There is a lack of direct evidence that these compounds are also human carcinogens. Nonetheless, many scientists concur with the IARC that, for practical purposes, these nitrosamines should be regarded as carcinogenic in humans." [24]

1982 The Third Annual Report on Carcinogens states that the amount of nitrosonornicotine, a tobacco-specific nitrosamine, in commercial U.S. tobacco products "is one of the highest values of an environmental nitroso compound reported in the literature." [25]

1983 In his concluding remarks at the 8th International Symposium on *N*-nitroso compounds, P.N. Magee stated that "[a] role for nitrosamines in the causation of human cancer has not been established, but it should not be excluded and merits further study." [26]

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1984 Although their data showed that increases in the nitrate content of cigarettes reduced the levels of "tar," nicotine, carbon monoxide, catechol and benzo[*a*]pyrene, Adams, Lee and Hoffman emphasize the significantly higher yields of volatile and tobacco-specific nitrosamines in the mainstream smoke of an 85 mm non-filter cigarette. The authors conclude that "[t]he findings of this model study support the recommendation that the nitrate content of tobacco products should be reduced." [27]

1984 Preussmann tabulated the ranges of reported levels of a variety of *N*-nitrosamines in tobacco and tobacco smoke (mainstream and sidestream). [28]

1985 The IARC concludes that tobacco-specific nitrosamines are the most abundant carcinogens in tobacco smoke. [29]

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